THE MEDICAL LETTER

a non-profit publication

on Drugs and Therapeutics

Published by Drug and Therapeutic Information, Inc., 136 East 57th Street, New York 22, New York

Vol. 3, No. 15 (Issue #66) July 21, 1961

COLY-MYCIN

Colistimethate sodium (Coly-Mycin - Warner, Chilcott), a polypeptide antibiotic derived from Aerobacillus colistinus and administered intramuscularly, has now been introduced in the United States after several years of use in Europe and Japan. In addition to foreign studies, several clinical and laboratory studies of Coly-Mycin have been reported in this country, and it appears to be a useful addition to the small group of antibacterial agents (polymyxin B, kanamycin and neomycin) available for the treatment of blood-stream and urinary-tract infections caused by strains of Pseudomonas, Aerobacter, and other gram-negative bacilli resistant to streptomycin, sulfonamides and broad-spectrum antibiotics.

Although Coly-Mycin is very similar to polymyxin B in structure and spectrum of bacterial action, the evidence so far indicates that it is less toxic. Animal studies and limited clinical studies also suggest that Coly-Mycin is less toxic than kanamycin and neomycin, though clinical data are inadequate for direct comparison of these antibiotics with respect to toxicity.

ACTIVITY - Most of the common gram-negative bacilli are inhibited by concentrations of Coly-Mycin which are readily achieved in the blood and which are exceeded in the urine even with moderate doses; and the ratio of bactericidal to inhibitory concentrations is quite low. With Aerobacter, Brucella, and Pseudomonas, however, from a quarter to a half of all strains require more than 5 mcg. per cc. for inhibition. Nearly all Proteus strains are resistant to Coly-Mycin, as they are to polymyxin B. Resistance of one strain of Aerobacter and one of Pseudomonas to Coly-Mycin has been induced in vitro (H. A. Hirsch, et al., Proc. Soc. Exp. Biol., N.Y., 103: 338, 1960), with cross-resistance to polymyxin B. In clinical use, the development of bacterial resistance or of cross-resistance with agents other than polymyxin B has not yet become a problem. Superinfections with resistant strains of Proteus and occasionally of Aerobacter have, however, occurred. Interestingly, overgrowth of Candida has not been observed.

Adequate information is lacking on the distribution of Coly-Mycin in the tissues; therefore, it is well to assume that like polymyxin B it has limited tissue distribution, and will not be useful in meningitis and in surgical and other infections which are outside the urinary tract and which are not accompanied by bacteremia. Nevertheless, in wound infections, meningitis, pneumonia or septicemia caused by gram-negative bacilli resistant to all other agents, Coly-Mycin may be

EDITORIAL BOARD: **Harold Aaron, M.D.**; **Lytt I. Gardner, M.D.**, Prof. of Pediatrics, State Univ. of N. Y., Upstate Medical Center; **Nicholas M. Greene, M.D.**, Prof. of Anesthesiology and Lecturer in Pharmacology, Yale Univ. Med. School; **Paul H. Lavietes, M.D.**, Assoc. Clin. Prof. of Med., Yale Univ. Med. School; *ADVISORY BOARD:* **Louis C. Lasagna, M.D.**, Assoc. Prof. of Med. and Director, Div. of Clin. Pharmacology, Johns Hopkins Med. School; **Desmond R. Laurence, M.D.**, Lecturer in Pharmacology, Univ. Coll. Hosp. Med. School, London; **George E. Moore, M.D.**, Assoc. Prof. of Surgery, Buffalo Univ. Med. School and Director, Roswell Park Memorial Inst.; **John T. Murphy, Phm.D.**, Director of Pharmaceutical Research and Development, Mass. General Hospital; **Maxwell M. Wintrobe, M.D.**, Prof. and Head of Dept. of Med., Univ. of Utah Coll. of Med; **Robert I. Wise, M.D.**, Prof. and Head of Dept. of Med., Jefferson Med. Coll.; *MANAGING DIRECTOR:* **Arthur Kallet.**

Copyright 1961, Drug and Therapeutic Information, Inc.

worth trying despite the comparative dearth of reliable data on its use in such infections. In acute Pseudomonas urinary-tract infections, the drug has clearly been shown to be effective, the results being predictable from in vitro susceptibility tests.

DOSAGE - The manufacturer recommends that Coly-Mycin be administered only intramuscularly in two to four divided doses totaling 1.5 to 5 mg. per kg. per day, but larger doses may be needed in severe infections. With a single injection serum concentrations reach a peak in about two hours, and the concentration is reduced about half in six hours. For most infections, adequate concentrations can probably be obtained with two doses not to exceed 5 mg. per kg. per day.

TOXICITY - The most important toxic effect, particularly in infants, has been mild azotemia with slight to moderate fever. There is no good evidence of an adverse effect on the hematopoietic tissues, but one case of leukopenia which may possibly have been caused by the antibiotic has been reported. Neurotoxicity has been mild, and eighth-nerve damage such as occurs with kanamycin and neomycin has not been reported. Occasional rashes have been noted.

Paresthesias around the mouth and tingling in the extremities have occurred in about five per cent of the patients in some series. Other annoying effects have been gastrointestinal disturbance, pruritus, transient vertigo and slurred speech. Pain at the site of injection also occurs. Despite the relatively low toxicity observed thus far, the possibility of more severe reactions, especially renal injury, cannot be discounted. Caution is especially needed when very large doses are used, as in the treatment of sepsis and pyelonephritis.

In summary, Coly-Mycin has the same indications for use as polymyxin B, with the apparent advantage, thus far, of a lesser risk of kidney and nervous-system toxicity. Since toxic effects may appear with longer use, however, and since resistant strains of bacteria may become a problem, the antibiotic should be reserved for severe infections by susceptible gram-negative bacilli and for urinary-tract infections by susceptible strains of Aerobacter and Pseudomonas organisms. (No antibiotic can be counted on to cure urinary-tract infections in which poor drainage or obstruction is involved.)

Coly-Mycin is available in vials containing 150 mg. of the antibiotic, 8 mg. of dibucaine hydrochloride to counteract the pain of injection, and citric acid and sodium citrate as buffers. Each vial is reconstituted with 2 cc. of sterile distilled water. The average effective daily adult dose of Coly-Mycin is 150 mg., which costs the physician about $10.

HALDRONE AND CELESTONE

Two new drugs — paramethasone acetate (Haldrone - Lilly) and betamethasone (Celestone - Schering), both analogues of methylprednisolone — have been added to the list of anti-inflammatory steroids available to physicians. (Haldrone is the 6-alpha-fluoro, 16-alpha analogue, and Celestone the 9-alpha-fluoro, 16-beta analogue.) The manufacturers of Haldrone call it "a significant achievement

in corticosteroid research," and Celestone is claimed to provide "enhanced anti-inflammatory effect with the use of lower dosages." Nevertheless, an examination of both published and unpublished clinical and metabolic reports and of the manufacturers' literature does not show that these new steroids offer significant advantages over prednisone and other corticosteroids either in effectiveness or in frequency or severity of side effects.

With all of the corticosteroids, the risk of certain toxic, metabolic and other unwanted effects is incurred, and with a new corticosteroid there is always the possibility of new side effects. Among the serious side effects encountered with all corticosteroids are demineralization of bone, disturbances of protein and carbohydrate metabolism, and serious mental aberrations. Cortisone and hydrocortisone are also responsible for retention of salt and water. Prednisone and the newer steroids have the advantage of producing less retention of salt and water, an advantage that marked an important advance in anti-inflammatory steroid therapy. But no other clear dissociation of objectionable effects from the desired anti-inflammatory effects has been obtained in any of the analogues of cortisone, including the new ones.

NEW SIDE EFFECTS - Certain of the analogues have shown peculiar or unusually severe side effects. Dexamethasone, initially reported to have a remarkably low incidence of side effects, has a greater tendency than other steroids to produce excessive mental stimulation and increased appetite. Triamcinolone sometimes produces striking muscular cramps, weakness, and even atrophy, much less evident with other steroids.

A study of clinical reports and discussion with Medical Letter consultants indicate that the range, incidence and severity of side effects with betamethasone and paramethasone thus far observed are about the same as with prednisone. No new side effects have yet been noted.

A new steroid which primarily duplicates the action of cortisone or prednisone may at times be useful, since a particular patient may respond better or with fewer or less severe side effects to one compound than to another. In the reports on Haldrone and Celestone, however, few instances are cited in which a better effect was obtained than that achieved with prednisone or prednisolone, and it is doubtful that therapeutic resources are particularly enriched by proliferation of corticosteroids differing mainly in milligram potency. Nevertheless, if no new or more severe side effects appear with longer use of these drugs, the physician may consider it worthwhile to try one of them when another steroid appears to be ineffective, or to have exceptionally severe side effects.

One very big difference among the various steroids is in milligram potency, but milligram potency has no clinical significance. Equivalent doses of the new and old corticosteroids are: cortisone, 25 mg.; hydrocortisone, 20 mg.; prednisone (Meticorten - Schering, and others), 5 mg.; prednisolone (Meticortelone - Schering, and others), 5 mg.; methylprednisolone (Medrol - Upjohn), 4 mg.; triamcinolone (Aristocort - Lederle; Kenacort - Squibb), 4 mg.; paramethasone (Haldrone), 2 mg.; dexamethasone (Decadron - Merck; Gammacorten - Ciba; Deronil - Schering), 0.75 mg.; betamethasone (Celestone), 0.6 mg.

MICRIN AND ORAL ANTIBACTERIAL AGENTS

Micrin (Johnson & Johnson), a combination of two quaternary ammonium compounds (dequalinium, 0.02 Gm. per liter, and cetyl pyridinium chloride, 0.25 Gm. per liter), is being heavily promoted as a mouthwash and gargle with claims of ability "to kill rapidly the bacteria found in the mouth associated with bad breath, minor sore throats, tooth decay and common gingival irritations," and "to give a long-lasting antibacterial action." The manufacturer's data on dequalinium indicate that in vitro this component of Micrin, like other quaternary ammonium compounds, has an inhibitory effect on many gram-positive and gram-negative bacteria, but with more prolonged action and greater potency against a test strain of Staphylococcus aureus than the standard quaternary, benzalkonium chloride.

VALUE OF MOUTHWASH - With any oral antiseptic mouthwash and gargle, claims relating to a reduction of the number of bacteria in the mouth need not be doubted, since the mechanical effects of rinsing the mouth with ordinary tap water will markedly reduce the number of oral bacteria temporarily. The only significant test of the value of such a product is its performance in human subjects. No convincing evidence is available, however, to support claims that Micrin has greater effect in preventing or controlling mouth odors or mouth and throat infections than the mechanical action of rinsing or gargling.

Bad breath is rarely if ever caused by ordinary oral bacteria. In some instances it is caused by aromatic substances (present in garlic, onions, etc.) which are absorbed from the gastrointestinal tract, carried through the pulmonary circulation and then exhaled in the breath. Occasionally, bad breath may be due to gastric retention, to severe liver or metabolic disorders, or to suppurative or necrotizing infections of the oral cavity or of the upper or lower respiratory tract. For such infections surgery and often antibiotics are required.

SORE THROAT - "Minor sore throat" usually requires no treatment if it is minor. Sore throat due to a virus would not be affected by any mouthwash or gargle, and a streptococcal sore throat requires antibiotic treatment for ten days. It has never been shown that any antiseptic gargle or mouthwash is effective in preventing or treating a sore throat. On the contrary, frequent use of an antiseptic mouthwash may adversely affect the normal bacteriostatic action of the saliva. A plain warm-water gargle, however, does help reduce the spasm of the muscles of the throat responsible for some of the pain associated with sore throat.

The claim that Micrin has a destructive effect on bacteria associated with tooth decay is meaningless in the absence of evidence showing that the use of Micrin has reduced tooth decay. Such effect has not been established with any mouthwash. Nor is there evidence that Micrin is useful in gingival disorders. The ineffectiveness of any such product in gingival disorders is emphasized in Periodontal Disease (W.H.O. Technical Report Series, No. 207, 1961), which says (p. 34): "Thorough rinsing with plain water helps to remove any debris loosened by the tooth-brushing. The addition of some weak antiseptic or flavouring agent may make this procedure more acceptable but not more efficacious." While toxic and sensitivity reactions to Micrin are not likely, the regular use of this mouthwash may cause the appearance of brownish stains on the teeth.

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS is published fortnightly by Drug and Therapeutic Information, a non-profit corporation, 136 E. 57th St., New York 22, N. Y. Second-class postage paid at New York, N. Y. Subscription fees: 1 yr., $12.50; 2 yrs., $23; 3 yrs., $34 ($6.25 per year for residents, interns, students).